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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/954,586	09/11/2001	Melissa M. Cunningham	GP116-03.UT	7245

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/954,586	CUNNINGHAM ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-23,29,37-40,50-53,59,60,84 and 87-159* is/are pending in the application.

4a) Of the above claim(s) *87-92,100-105,108-113,127-132 and 145-150* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-23,29,37-40,50-53,59,60,84,93-99,106,107,114-126,133-144 and 151-159* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0303* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *1449: 1/25/02* .

DETAILED ACTION

1. This action is in response to the papers filed December 19, 2002. Currently, claims 1, 6-23, 29, 37-40, 50-53, 59-60, 84, 87-159 are pending.

2. Claims 87-92, 100-105, 108-113, 127-132, 145-150 are withdrawn from consideration, as drawn to non-elected subject matter.

Election/Restrictions

3. Applicant's election without traverse of SEQ ID NO: 6, 10, 14, 18, 29, 33, 37, 41, 48, 54, 60, 66 in Paper filed December 19, 2002 is acknowledged.

Priority

4. This application claims priority to U.S. Provisional Application No. 60/232,028, filed September 12, 2000.

Drawings

5. The drawings are acceptable.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

For example, page 31, contains a hyperlink.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 6-23, 29, 37-40, 50-53, 59-60, 84, 93-99, 106-107, 114-126, 133-144, 151-159 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to probes, primer and methods for detecting *Cryptosporidium parvum.*

The specification has provided specific sequences of SEQ ID NO: 6, 29, 48 for use in detecting *Cryptosporidium parvum* but not nucleic acids derived from non-*Cryptosporidium parvum* organisms including *Cryptosporidium muris, Cryptosporidium baileyi or Cryptosporidium wrairi.*

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43

USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, there is no actual reduction to practice of the claimed invention, clear depiction of the claimed invention in the drawings or complete detailed description of the structure. A review of the language of the claim indicates that the claim is drawn to a genus, i.e., any nucleic acid that minimally hybridizes to a nucleic acid derived from a *Cryptosporidium parvum* organism in a test sample having at least 10 contiguous bases which is at least 80% complementary to the target sequence of SEQ ID NO: 1. The partial structure provided within the claim broadly encompasses variant 18S rRNA, homologous 18S rRNA and nucleic acid sequences yet to be discovered. There is substantial variability among the species of DNAs encompassed within the scope of the claims because a nucleic acid which hybridizes to a nucleic acid derived from a *Cryptosporidium parvum* organism in a test sample having at least 10

contiguous bases which is at least 80% complementary to the target sequence of SEQ ID NO: 1 is only a fragment. A description of a genus of nucleic acids may be achieve by means of a recitation of a representative number of nucleic acids, defined by nucleotide sequence, falling within the scope of the gnus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Therefore, weighing all factors, 1) partial structure of the DNAs that hybridizes to a nucleic acid derived from a *Cryptosporidium parvum* organism in a test sample having at least 10 contiguous bases which is at least 80% complementary to the target sequence of SEQ ID NO: 1, 2) the breadth of the claim, 3) the lack of correlation between the structure and function; in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of nucleic acids hybridizes to a nucleic acid derived from a *Cryptosporidium* organism in a test sample having at least 10 contiguous bases which is at least 80% complementary to the target sequence of SEQ ID NO: 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

> granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 6, 7, 19, 20-22, 93 are rejected under 35 U.S.C. 102(a) as being anticipated by Nelson (Genbank Accession Number AA167899, August 23, 2000).

Nelson teaches a nucleic acid from Cryptosporidium parvum 18S ribosomal RNA gene. The nucleic acid of Nelson comprises SEQ ID NO: 6. Therefore, the nucleic acid of Nelson is a probe comprising an oligonucleotide which hybridizes to SEQ ID NO: 6. The nucleic acid of Nelson would not hybridize to a non-*Cryptosporidium parvum* organisms including *Cryptosporidium muris, Cryptosporidium baileyi or Cryptosporidium wrairi* under certain stringency conditions. Thus, the nucleic acid of Nelson anticipates the limitations of the instant claims.

9. Claims 1, 6, 7, 19, 20-22, 93 are rejected under 35 U.S.C. 102(e) as being anticipated by Wick et al. (US Pat. 6,063,604, May 16, 2000).

Wick teaches a nucleic acid from Cryptosporidium parvum 18S ribosomal RNA gene. The nucleic acid of Wick comprises SEQ ID NO: 6. Therefore, the nucleic acid of Wick is a probe comprising an oligonucleotide which hybridizes to SEQ ID NO: 6. The nucleic acid of Wick would not hybridize to a non-*Cryptosporidium parvum* organisms including *Cryptosporidium muris, Cryptosporidium baileyi or Cryptosporidium wrairi* under certain stringency conditions. Thus, the nucleic acid of Nelson anticipates the limitations of the instant claims.

10. Claims 1, 6-7, 19-23, 29, 93-99, 106-107, are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Pat. 5,474,796, December 12, 1995).

As written, the claims are directed to a probe comprising at least 10 contiguous base region which is at least 80% complementary to SEQ ID NO: 1. While the claim requires that the probe does not hybridize to a nucleic acid from a non-*Cryptosporidium* organism under stringent conditions, the claim implies that a 10-mer exists which is encompassed by the instant claims. Applicant is reminded that MPEP 2112.01 teaches "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.'" The instant probes appears to be identical in structure to the claimed probes. The claimed probes are directed to 10-mers which identify *Cryptosporidium*.

Brennan teaches oligonucleotides having 10 nucleotides each (10-mer). The oligonucleotides of Brennan represents every possible permutation of the 10-mer oligonucleotide.

Therefore, since Brennan teaches every limitation of the instant claims, Brennan anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 6-10, 14, 19-23, 29, 37-40, 50-53, 59-60, 84, 93-99, 106-107, 114-126, 133-144, 150-159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (J. of Infectious Disease, Vol. 177, pages 1443-1446, 1998) in view of Williams et al. (US Pat. 6,146,855, November 14, 2000) and Xiao et al. (Applied and Environmental Microbiology, Vol. 65, No. 8, pages 3386-3391, August 1999) in view of Hogan (US Pat. 5,595,874, January 1997).

The broad product claims have also been rejected in this 103 rejection in the event that the claims were amended to narrow the claims to recite consisting of SEQ ID NO: 1, 21, 22, for example.

Zhu et al. (herein referred to as Zhu) teaches a method of detecting *Cryptosporidium* using genus specific primers from the 18S rRNA. The target DNA for PCR was the small subunit rRNA gene (srDNA).

Zhu does not specifically teach using SEQ ID NO: 6 as a target sequence for the probes and primers.

However, Williams et al. (herein referred to as Williams) provides an alignment for the relatedness in Figure 3A between *C. parvum, C. muris, C. baileyi.* The positions of specific *C. parvum* 18S rRNA probes in respect of the whole 18S rRNA sequence is illustrated. SEQ ID NO: 6, 29, 48 are embedded within the sequences.

Moreover, Xiao et al. (herein referred to as Xiao) teaches a comparison study of seven Cryptosporidium various isolates from various hosts. The species include *C. parvum, C. wrairi, C. muris* and *C. baileyi.* Xiao teaches that the nucleotide sequences of the parasites were deposited in GenBank under various accession numbers. Xiao teaches aligning the sequences and identifying differences among the isolates.

Moreover, Hogan teaches a method which compares one or more sequence rRNA variable regions from a target organism to one or more rRNA variable region sequences from closely related species that can be utilized to distinguish between such organisms. Hogan teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers,

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (col. 10, lines 13-15)(limitations of Claims 4-6). Oligonucleotides complementary to sequences adjacent to the probe regions were synthesized and used in the hybridization mix according to Hogan et al., U.S. Pat. No. 5,030,557; filed Nov. 24, 1987, entitled "Means and Method for Enhancing Nucleic Acid Hybridization (the "helper " patent application). Hogan teaches that oligonucleotide probes may be labeled by any of several well known methods such as radioisotopes, non-radioactive reporting groups, non-isotopic

materials such as fluorescent molecules (col. 10, lines 45-60). Hogan teaches that probes may be labeled using a variety of labels, as described within, and may be incorporated into diagnostic kits(limitations of Claims 74, 88, 135-155).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the genus specific PCR primers taught by Zhu using the alignment provided by Williams and Xiao and the specific guidance provided by Hogan to obtain the invention as a whole. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent functional equivalents of the probes and primers of Zhu, a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. The specific probes, absent any unexpected results with the instantly claimed SEQ ID NO:s, the instantly claimed genus-specific probes are considered to be functionally equivalent to those of Zhu because they are located within the same region, namely the 18S rRNA as the instantly claimed oligonucleotides and those of Zhu and further because Mhu

teaches the usefulness of the 18S region for detecting and distinguishing between *C. parvum, C. muris, C. baileyi* , and *C. wrairi*. The art also teaches that one of skill in the ad can modify the disclosed genus specific primer to enhance the properties based on factors such as probe length, melting temperature, and sequence content. Additionally, at the time the invention was made, the sequence of the Cryptosporidium nucleic acids of distinct types were known and it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made and within the skill of the art to obtain the instantly claimed oligonucleotides following the teachings of Hogan as to the identification of sequences that are genus specific and thus useful for the identification of Cryptosporidium by hybridization. Further, the teachings of Zhu, Williams, Xiao and Hogan indicate that the state of the art at the time the invention was made would have led one of ordinary skill in the art to the claimed genus-specific probes because Zhu, Williams, Xiao and Hogan teaches the usefulness of the 18S region of the Cryptosporidium for species-specific probes, species-specific primers and further teaches methods in which the probes may be modified.

13. Claims 11-13, 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu et al. (J. of Infectious Disease, Vol. 177, pages 1443-1446, 1998) in view of Williams et al. (US Pat. 6,146,855, November 14, 2000) and Xiao et al. (Applied and Environmental Microbiology, Vol. 65, No. 8, pages 3386-3391, August 1999) in view of Hogan (US Pat. 5,595,874, January 1997) as applied to Claims 1, 6-10, 14, 19-23, 29,

37-40, 50-53, 59-60, 84, 93-99, 106-107, 114-126, 133-144, 150-159 above, and further in view of Becker et al. (US Pat. 6,361,945, March 26, 2002).

Neither Zhu, Williams, Xiao or Hogan specifically teach a method using interacting labels including luminescent label and quencher labels.

However, Becker teaches a method of using "molecule torches" for detecting the presence of a target nucleic acid sequence. Becker teaches the molecular torches contain a target binding domain, a target closing domain and a joining region (col. 2, lines 15-25). The target binding domain is biased towards the target sequence. A luminescent/quencher pair is preferably used (col. 9, lines 45-60)(limitations of Claims 11-12). Moreover, Becker teaches using 2'-methoxy substituted ribonucleotides (col. 10, lines 55-65)(limitations of Claim 13). Becker teaches "one of the advantages of using the present invention in conjunction with a transcription-associated amplification is that the molecular torch can be added prior to amplification, and detection can be carried out without adding additional reagents (col. 12, lines 10-20). Becker teaches using pseudo peptide backbones (col. 8)(limitations of Claim 14).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the PCR detection assay of Hogan to encompass the use of molecular torches of Becker. Becker teaches that there are numerous means for detecting probes designed to preferentially hybridize to the target sequence. Therefore, the method of Becker is an equivalent method as the method of Hogan which enables the detection of nucleic acid binding.

Conclusion

14. No claims allowable.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
June 28, 2003

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